REMARKS

Amendments to the Specification

Obvious clerical errors noted in paragraphs **[0020]**, **[0039]** and **[0067]** are hereby corrected. Support for these amendments is found in the original paragraphs.

Personal Interview with Examiners

Applicants gratefully acknowledge the cordial personal interview held April 26, 2007, among Examiners Kishore and Oh and their undersigned counsel. The following remarks are respectfully submitted to reflect the discussion that took place at the interview.

Enablement

Reconsideration of the rejection of claims 1 and 3-67 under 35 U.S.C. §112, first paragraph, for supposed lack of enablement, is respectfully requested.

The Office Action properly acknowledges that the application is enabling at least for tramadol and promethazine, but argues that the application lacks evidence that demonstrates enablement over the full scope of the presently claimed invention so that undue experimentation would be required from a person skilled in the art in order to carry out the present invention over its full scope. Applicants respectfully disagree. The asserted basis for the rejection is neither correct nor consistent.

According to the present invention, it has been found that controlled release of an active substance from an oral dosage form can simply be achieved by combining two or more different salts of the same active substance having different water solubilities in a common dosage form from which the active ingredient is released by dissolution of the salts. This simple and elegant principle of achieving controlled release of an active substance is shown in detail in the

specific examples of the present application, where it was demonstrated that different salts of tramadol, e.g., tramadol hydrochloride and tramadol saccharinate or of promethazine have different release profiles and that a common dosage form comprising these salts has a release profile different from either one of the single substance release profiles.

The release profile or liberation profile for the active substance was determined using the basket method according to European Pharmacopoeia (see paragraph [0067] of US 2002/10176888). This is a standard test method commonly used among those skilled in the art in order to investigate the active substance liberation behavior of dosage forms intended for oral administration. From the results of the representative tests described in the specification, it follows that it is possible to adjust the drug release profile of an oral dosage form by combining different salts of one and the same active substance in a common oral formulation. Based on these test results, the Examiner has rightfully come to the conclusion that the present invention is properly enabled for the active substances tramadol and promethazine.

It should thereby be noted that the test evidence that establishes the operability of the invention does not address questions of bioavailability. Indeed, bioavailability is not at issue in the claimed invention. Instead, the invention is simply directed to the strictly physical process of controlling release (i.e., liberation) of the active substance from the dosage form by dissolution of salts with different water solubilities. This is simply a physical phenomenon dependent on the differing water solubilities of the different salts that are used and does not involve bioavailability or any other physiological phenomenon.

The same standards of enablement apply to salts of other active ingredients. While the pharmacological properties of various active substances may be unpredictable in some cases, the physical properties of salt formation, the fact that salts with different counter ions will have different solubilities, and the physical phenomenon of dissolution of a salt are well known and quite predictable. At most, only minimal screening to determine the relative solubilities of

different salts would be necessary for a person skilled in the art to practice the invention with any active ingredient. These physical principles are applicable to all salts.

As for the compatibility with pharmaceutical excipients, it is considered to be within the professional expertise of persons skilled in the art of preparing pharmaceutical formulations to determine the compatibility of salts of active ingredients with known pharmaceutical excipients. Indeed, this is a routine matter for such professionals.

The working examples in the application illustrate in detail how to carry out the claimed invention with representative compounds tramadol and promethazine. The phenomena of salt formation and dissolution in aqueous media are strictly physical phenomena and are not subject to the vagaries and unpredictabilities of physiological phenomena. The procedure described for the representative examples thus is fully applicable to and can be used by a person skilled in the art for other active ingredients that form salts with a reasonable expectation of success.

Given the universality and predictability of the known phenomenon of salt formation and the known fact that salts with different counter ions will have different solubilities, a person skilled in the art would have no difficulty whatsoever applying the principle of the invention to any active ingredient to control the release from a pharmaceutical dosage form. As recognized in concluding that tramadol and promethazine are enabled, bioavailability is not the issue.

At the interview, the Examiners acknowledged that use of at least two salts with the different water solubilities could result in a modified overall release rate from an appropriate formulation, but noted that the claim language "solid aggregation state" was sufficiently broad to read on a mere mixture of two powders from which the active ingredient could be released by simple dispersion of the undissolved powders. The claim has, therefore, been amended to more clearly define how the claimed oral dosage form allows differential drug release by reciting that release is effected by dissolution of the salts of the active

ingredient. Support for this amendment is found, *inter alia*, in lines 7-9 of paragraph [0037] of the specification where it is pointed out that the active substance is not released from the dosage form until it reaches the intestinal tract because it passes through the gastric tract undissolved. See also paragraph [0007] of the specification.

In view of the foregoing, reconsideration and withdrawal of the enablement rejection are respectfully requested.

Novelty

The rejection of claims 1, 3-5, 15, 17, 18, 21, 30-32 and 62-67 under 35 U.S.C. §102(e) over Burnside, *et al.*, US 6,322,819 (hereinafter "Burnside"), is respectfully traversed.

Burnside merely discloses a multiple pulsed dose drug delivery system for amphetamine salts, comprising an immediate-release component and an enteric delayed-release component. Accordingly, the dosage forms of Burnside require the presence of delayed-release material and, therefore, further formulation measures.

In contrast to this, the dosage forms of the presently claimed invention allow *for* controlled release *of an active* substance, simply by combining two or more different salts of one and the same active substance, without the need for use of further controlled release materials or additional formulation steps.

Moreover, when Burnside refers to dosage forms comprising more than one amphetamine salt, this does not signify that one and the same active substance is present with different counter ions (as in the dosage forms of the present invention). Rather, these statements in Burnside indicate that salts of different amphetamines are present, not the same amphetamine with different counter ions (see col. 3, lines 1-3; col. 7, lines 48-55).

In addition, there is not the slightest intimation in Burnside of salts of the same active substance with two different counter ions that have water

solubilities that differ from each other by at least a factor of 2 as required by the instant claims.

It follows that Burnside does not disclose a dosage form comprising two or more different salts of one and the same active substance as claimed. Thus, Burnside does not anticipate the presently claimed invention.

Obviousness

Finally, the rejection of claims 1, 3-9, 11, 12, 15, 17, 18, 21, 30-32, 55-58 and 62-67 under 35 U.S.C. §103(a) over Oshlack, *et al.*, WO 99/01111 (hereinafter "Oshlack"), is also respectfully traversed.

Oshlack discloses oral sustained release solid dosage forms of tramadol having extended release over at least 24 hours. Controlled release from these dosage forms is achieved via the use of a matrix of a hydrophobic material and elaborate formulation steps, e.g., curing within a certain temperature range.

However, it was exactly the object of the present invention to provide oral dosage forms of an active substance that allow for controlled release of the active substance without the need for using elaborate separate formulation steps to adjust the liberation profile of said active substance.

There is not the slightest hint in Oshlack that controlled release of an active substance could be achieved without the use of certain controlled release agents such as hydrophobic materials or certain formulation measures, such as curing within a certain temperature range. In particular, there is no hint that controlled release from oral dosage forms can simply be achieved by combining two or more different salts of one and the same active substance, thereby adjusting a desired release or liberation profile of the active substance as claimed in the present application without elaborate formulation steps.

The rejection cites old CCPA decisions holding it *prima facie* obvious to combine two compositions, each of which is taught by the prior art to be useful for the same purpose. However true this may be regarding mixtures of two different pharmaceutically active agents, the logic breaks down and is not

applicable to mixtures of two different salts of the same active agent as claimed in the present invention. The record is devoid of any example of such a mixture, and with good reason. The formation of a mixture of two different salts of the same active ingredient is unquestionably more troublesome and inconvenient than the provision of a single salt. There is nothing in the record that would lead a person of skill in the art to expect any advantage from using a mixture of two materials over using a single material when there is only one active ingredient present in the mixture. All that the prior art would lead a person of ordinary skill in the art to expect would be that such a mixture of salts of the same active ingredient would have the same effect as a single salt of the active ingredient. Oshlack gives a person of ordinary skill in the art no reason or motivation to form such a mixture of salts of the same active ingredient having different solubilities. Accordingly, it cannot be fairly said to be obvious for a person of ordinary skill to incur the trouble and inconvenience of forming such a mixture for no reason.

It is only the Applicants who have recognized that unexpected advantages of extended activity could be attained from using a mixture of at least two different salts of the same active ingredient having different solubilities as claimed in the present invention. Consequently, it is only after a consideration of the Applicant's disclosure that there is any reason or motivation to form such a mixture. However, such hindsight consideration is clearly improper.

The cited prior cases dealing with mixtures of different active agents known to be useful for the same purpose are inapposite because their facts are different. Two different active agents can be presumed to have some differences in activity so that the combination of the two could be expected to yield a broadened spectrum of activity. The same is **not** true for two different salts of the same active ingredient. Consequently, the reasoning of cases dealing with combinations of two different active agents is not applicable to the present invention, which deals with a combination of at least two different salts of the same active agent having different solubilities.

Obviousness is not susceptible of determination by rote application of mechanical rules derived from cases with different facts. Rather, obviousness in any given case must be decided on the facts of that case. *In re Jones*, 21 USPQ2d 1941 (Fed. Cir. 1992) ("Every case, particularly those raising the issue of obviousness under section 103, must necessarily be decided upon its own facts."); *Ex parte Goldgaber*, 41 USPQ2d 1172 (B.P.A.I. 1995) ("Again, each case under 35 USC 103 must be decided on its own particular facts."). Under the facts of this case, since the state of the art provides no motivation to make a combination of at least two different salts of the same active ingredient having different solubilities as claimed, the obviousness rejection is not well founded. Thus, Applicants respectfully submit that their presently claimed invention is not obvious in view of the cited Oshlack PCT publication, and reconsideration and withdrawal of the rejection are, therefore, respectfully requested.

At the interview, the Examiners acknowledged that the prior art in the rejections of record do not appear to teach the concept of a mixture of two salts of the same active ingredient with differing solubilities. The Examiners, therefore, indicated that the prior art rejections over Burnside, *et al.* (US 6,322,819) and Oshlack, *et al.* (WO 99/01111) would be reconsidered and withdrawn.

Conclusion

For the foregoing reasons, the application is respectfully submitted to be in condition for allowance, and prompt, favorable action thereon is earnestly solicited.

Moreover, in view of the fact that withdrawn claims 10, 13, 14, 16, 19, 20, 22-29, 33-54 and 59-61 all depend from and are linked by allowable claim 1, rejoinder and allowance of these claims are also respectfully requested.

If there are any questions regarding this amendment or the application in general, a telephone call to the undersigned at (202) 624-2845 would be appreciated since this should expedite the examination of the application for all concerned.

If necessary to effect a timely response, this paper should be considered as a petition for an Extension of Time sufficient to effect a timely response, and please charge any deficiency in fees or credit any overpayments to Deposit Account No. 05-1323 (Docket #029310.50986).

Respectfully submitted,

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